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AF/1635

PTO/SB/21 (02-04)

Approved for use through 07/31/2006. OMB 0651-0031

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Total Number of Pages in This Submission

38

Application Number	09/918,026
Filing Date	July 30, 2001
First Named Inventor	Crooke et al.
Art Unit	1635
Examiner Name	T. Gibbs
Attorney Docket Number	ISPH-0588

ENCLOSURES (Check all that apply)

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| <input checked="" type="checkbox"/> Fee Transmittal Form
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Customer No. 36441

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	HOWSON AND HOWSON Mary E. Bak
Signature	<i>Mary E. Bak</i>
Date	August 23, 2004

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Signature	<i>Kelly A. Karstaedt</i>	Date	August 23, 2004
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This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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AUG 25 2004

PTO/SB/17 (10-03)

Approved for use through 07/31/2006. OMB 0651-0032

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$ 165.00)

Complete if Known

Application Number	09/918,026
Filing Date	July 30, 2001
First Named Inventor	Crooke et al.
Examiner Name	T. Gibbs
Art Unit	1635
Attorney Docket No.	ISPH-0588

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit Account:Deposit Account Number
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) (\$ 0.00)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims		Extra Claims		Fee from below		Fee Paid	
Independent Claims		-20** =		X		=	
Multiple Dependent		-3** =		X		=	

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$ 0.00)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex parte reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$ 165.00)

SUBMITTED BY

(Complete if applicable)

Name (Print/Type)	Mary E. Bak	Registration No. (Attorney/Agent)	31,215	Telephone	215-540-9200
Signature	<i>Mary E. Bak</i>	Date	August 23, 2004		

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ISPH-0588

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. : 09/918,026 Confirmation No.: 1035
Appellant : Crooke et al.
Filed : July 30, 2001
TC/A.U. : 1635
Examiner : T. Gibbs
Customer No. : 36441
Title : ANTISENSE MODULATION OF ACYL COA
CHOLESTEROL ACYLTRANSFERASE-2 EXPRESSION

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BRIEF ON APPEAL

Sir:

This Brief on Appeal is timely filed in triplicate. A Notice of Appeal was filed on June 21, 2004, to which an Appeal Brief is due August 23, 2004 (August 21, 2004 falling on a Saturday), from the final rejection dated March 22, 2004, which rejected the pending claims 1, 4-10, 12, and 13. The fee of \$165 under 37 CFR § 1.17(c) for filing the Brief on Appeal is attached hereto.

Certificate Under 37 CFR § 1.8

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Kelly A. Karstardt
Signature
Kelly A. Karstardt

(1) Real Party in Interest

The inventors of the subject matter of this application have assigned the rights of the invention to ISIS Pharmaceuticals, Inc. The Assignment was recorded on February 13, 2002 at Reel 012619, Frame 0788.

(2) Related Appeals and Interferences

Appellants are not aware of any related appeals or interferences that may be related to the present application.

(3) Status of the Claims

Claims 1, 4-10, 12, and 13 were rejected in the Office Action dated March 22, 2004 and made final. These claims are the subject of this appeal. Claims 2-3, 11, and 14-20 were canceled during the course of the prosecution of this application.

(4) Status Amendments

There are no outstanding claim and/or specification amendments. The Examiner indicated in the Office Action dated March 22, 2004 that the arguments filed pursuant to 37 CFR § 1.111 on December 30, 2003 were not persuasive and the rejection of the claims under 35 USC § 103(a) was maintained.

There is, however, an outstanding issue regarding the consideration of documents timely filed in the Information Disclosure Statement dated March 31, 2003 and refiled on June 18, 2004. Specifically, the Examiner indicated in the

Office Action dated September 9, 2003 and March 22, 2004 that documents AQ and BQ would not be considered.

Since document BQ is in the English language and was properly listed in the Information Disclosure Statements, Appellants respectfully request that document BQ be considered on its face and that document AQ be considered to the extent of the comments provided therefor.

(5) Summary of the Invention

The present invention is drawn to antisense oligonucleotides targeted to a coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO: 3). The oligonucleotides not only hybridize within the sequence of SEQ ID NO: 3 and inhibit expression of the ACAT-2 protein, but do so at a minimum inhibition level of 40%.

The oligonucleotides of the present invention are 8-50 nucleobases in length. The specification of the present application demonstrates at least 15 examples of antisense sequences that fall under this requirement.

(6) Issues

Following consideration of the 37 CFR § 1.111 Response and Amendment, for which the Examiner stated that the arguments are not persuasive, the rejection of all of the pending claims under 35 USC § 103(a) is maintained.

The issue in this appeal is whether claims 1, 4-10, 12, and 13 are patentable under 35 USC § 103(a) over Cases et al. (International Patent Publication No. WO 99/67368) in view of Bennett et al. (US Patent No. 6,613,567) and

Fritz et al. (J. Colloid and Interface Sci., 1997, 195:272-288).

(7) **Grouping of the Claims**

Appellants believe that all of the pending claims should be considered together in assessing patentability.

(8) **Arguments**

The combination of Cases, Bennett and Fritz does not teach or suggest Appellants' invention.

Specifically, Cases in combination with Bennett and Fritz does not provide a reasonable expectation of success which is required to render the present invention obvious.¹ Appellants, with respect, rebut the Examiner's conclusion that with regard to ACAT-2, this cited art provides an **expectation of success** in obtaining antisense oligonucleotides capable of inhibition expression of ACAT-2 by 40%.²

Bennett and Fritz are cited for "generic" teachings related to antisense compounds. Neither is directed to antisense oligonucleotides to ACAT-2.

¹ In re Vaack, 947 F. 2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under 35 USC § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success."

² Page 6, lines 8-13 of the March 22, 2004 Office Action.

Cases refers to nucleic acid compositions encoding acyl CoA:cholesterol acyltransferase (ACAT) polypeptides, the polypeptide products (e.g., ACAT-2) produced thereof, and methods of making the same. Cases also provides the coding sequence of the human ACAT-2 gene as SEQ ID NO:2.

As admitted by the Examiner³, SEQ ID NO:2 of Cases is not identical to SEQ ID NO:3 of Appellants' invention, and is in fact missing approximately 60 nucleotides of the coding sequence of human ACAT-2. Further, the Examiner also acknowledged that Cases does not discuss a compound targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 that hybridizes with and inhibits expression of human acyl CoA cholesterol acyltransferase by at least 40% or such antisense oligonucleotides modified as specified by the present dependent claims.⁴

There is no way for anyone of skill in the art to predict whether one may obtain any particular percentage of inhibition simply by prior knowledge of generic antisense technology, (i.e., that fact that for completely unrelated genes, high levels of expression have been obtained), coupled with a known target sequence. Appellants' respectfully submit that there is nothing ***in this combination of prior art*** that suggests such success ***with ACAT-2 would be expected***. One of skill might be motivated to "hope for" such a level of success using generic

³ Page 5, line 21 through page 6, line 2 of the March 22, 2004 Office Action.

⁴ Page 6, lines 4-8 of the March 22, 2004 Office Action.

technology. However, nothing in the prior art allows for such an expectation. Only the present invention identifies that antisense oligonucleotides to ACAT-2 may be provided that inhibit expression by at least 40%. The only source of the required motivation to make and use antisense compounds directed to specific sequences of ACAT-2 is provided by the Appellants' own specification. Obtaining the motivation for combination of the prior art cannot properly be provided by Appellants' own disclosure.⁵

As demonstrated by Appellants, there are "antisense" sequences that may hybridize to the ACAT-2 coding sequence, but that provide no inhibition at all or that provide only low levels of inhibition. See, Tables I and II. Therefore, a general reference to the desirability of antisense sequences in Cases does not provide sufficient teachings to suggest the present invention. Since the modifications suggested by Bennett and Fritz are only generic comments, or teachings directed to MRP or HER-2, these references also do not provide the necessary teachings to suggest the presently claimed invention alone or in combination with Cases. Nothing in these references points to antisense sequences of ACAT-2 that are capable of generating at least 40% inhibition vs. sequences that generate lesser or no inhibition of expression.

Further, with regard to these combined references suggesting that antisense sequences to ACAT-2 are

⁵ *In re Oetiker*, 977 Fd 1443, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992) "There must be some reasons, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the Appellant's invention itself."

desirable, this is simply a suggestion that it may be obvious to try to obtain such sequences. An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target ACAT-2, simply because others have made antisense compounds to other *unrelated* proteins and that antisense sequences to ACAT-2 would be desirable, if made. The US patent law has long held that the "obvious to try" standard is not the appropriate standard for a determination of patentability.

The mere fact that this prior art may be modified in the manner as suggested by the Examiner does not make the modification obvious, unless the prior art suggested the desirability of the modification.⁶ As discussed above, the prior art references in combination and taken as a whole⁷ do not suggest the claimed invention.

None of the cited art provides any direction at all to indicate what sequences, if any, may be characterized by such a claimed level of inhibition of ACAT-2. Cases provides no direction at all regarding level of inhibition of ACAT-2. Fritz's discussion of carriers for oligonucleotides is not at all directed to inhibition level at all. The results of antisense studies in Bennett, show that only 12 of 39 tested oligonucleotides and 31 of 39 tested oligonucleotides that hybridized to the unrelated

⁶ *In re Fritch*, 23 USPQ2d 1780, 1783-1784 (Fed. Cir. 1992), citing *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

⁷ *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F. 2d 1044, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988) "Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination."

gene HER-2, were able to meet that level of inhibition. This result with HER-2 does not permit one of skill in the art to be able to predict Appellants' results with antisense sequences to ACAT-2, in which 15 of 23 oligonucleotides tested resulted in oligonucleotides meeting the required inhibition level of 40%.

There is no way to predict what target sequences the person of skill in the art would have used to generate results, and thus no way to predict Appellants' results *a priori*. For example, if the person of skill in the art, for example, performed generic antisense technology techniques on Cases' sequence, that person may have obtained Appellants' SEQ ID NOS: 40, 50 or 55, which demonstrate little inhibition.

In fact, Appellants' assignee, which is a company that specializes in antisense technology and uses the latest in bioinformatics programs, have demonstrated repeatedly that one may investigate 80 or more oligonucleotides in attempts to identify a target site permitting inhibition at a specific high level for a specific gene. One cannot anticipate similar results when one looks at completely different genes. One of skill in the art cannot *a priori* expect ease of target identification simply by knowing antisense methodologies and the gene sequence.

To make an obviousness rejection, the Examiner may review the combined teachings of the cited prior art, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole.⁸ However, the

⁸ *In re Kotzab*, 217 F. 3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

courts have held that this range of sources does not diminish the requirement for actual evidence. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence.^{9,10} Such a showing must be clear and particular.

With respect, no such clear and specific suggestion is made by the above combination that would make obvious the composition of claim 1 and its dependent claims. First, claim 1 and its dependent claims recite a **specific** gene, ACAT-2, as well as antisense oligonucleotides having a specific minimum inhibitory effect. Taking each reference as a whole, this combination does not provide any suggestion of the composition of claim 1.

Appellants maintain that the combination of the cited prior art, when the teachings are taken as a whole, fails to supply both clear and specific suggestions and evidence which provide both motivation **and a reasonable expectation of success** required to set forth obviousness of the pending claims.

Appellants believe that the Examiner continues to improperly use hindsight to construct the outstanding

⁹ *In re Dembiczak*, 50 USPQ2d 1614, 1616-1617 (Fed. Cir. 1999): "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight. ..."

¹⁰ *In re Lee*, 277 F. 3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002).

obviousness rejection, and has failed to interpret the prior art as a whole, from the point of view of a person having ordinary skill in the art at the time the invention was made, as required by 35 USC § 103.¹¹

Reversal of the outstanding rejection of pending claims 1, 4-10, 12, and 13 under 35 USC § 103(a) is respectfully requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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¹¹ *In re Fine*, 837 F. 2d 1081, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)
"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art of deprecate the claimed invention".

(9) AppendixThe Claims on Appeal:

1. An antisense oligonucleotide 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO: 3), wherein said compound specifically hybridizes with said region and inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40%.

4. The antisense oligonucleotide of claim 1 which comprises at least one modified internucleoside linkage.

5. The antisense oligonucleotide of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage.

6. The antisense oligonucleotide of claim 1 which comprises at least one modified sugar moiety.

7. The antisense oligonucleotide of claim 6 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

8. The antisense oligonucleotide of claim 1 which comprises at least one modified nucleobase.

9. The antisense oligonucleotide of claim 8 wherein the modified nucleobase is a 5-methylcytosine.

10. The antisense oligonucleotide of claim 1 which is a chimeric oligonucleotide.

12. A composition comprising the antisense oligonucleotide of claim 1 and a pharmaceutically acceptable carrier or diluent.

13. The composition of claim 12 further comprising a colloidal dispersion system.